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EXAMINER	
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ART UNIT	PAPER NUMBER
1639	24

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Please find below and/or attached an Office communication concerning this application or proceeding.

file copy

Office Action Summary	Application No.	Applicant(s)	
	09/430,735	EKWURIBE ET AL.	
	Examiner	Art Unit	
	Bennett Celsa	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *46-50,61-63,70,71 and 73-97* is/are pending in the application.

4a) Of the above claim(s) *26-35,50,61-63,84,86-93 and 95-97* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46-49,70,71,73-83,85 and 94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *23*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendment

Applicant's amendment dated 9/29/03 in paper no. 22 is acknowledged.

Information Disclosure Statement

The Information Disclosure statement (IDS PTO-1444 form) dated 9/29/03 in paper no. 23 is acknowledged. Please find attached an initialed PTO-1449 indicating Examiner consideration of the reference enumerated thereon.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

Claims 46-50, 61-63, 70-71 and 73-97 are currently pending.

Claims 46-49, 70-71, 73-83 , 85 and 94 are under consideration.

Claims 26-35, 50, 61-63, 84, 86-93 and 95-97 are withdrawn from consideration as being directed to a nonelected invention.

Election/Restriction

2. Applicant's election without traverse of Group II (claims 46-52) without traverse in Paper No. 6 is acknowledged. Claims 51-52 were subsequently canceled by applicant. New claims 70, 71 and 73-97 subsequently added read on the elected invention.

3. Claims 26-35 and 61-63 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention (and/or being drawn to canceled embodiments as in claims 61-63).

4. Applicant's election without traverse of Met-Enk (Lys)(PEG_4)$(CH2)_{13}CH_3$ (E.g. Lys modified Met-Enk with hydrophilic PEG and hydrophobic alkyl) which reads on claims 46-49, 70-71, 73-83 , 85 and 94 is acknowledged.

5. Claims 50, 84, 86-93 and 95-97 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention (and/or being drawn to canceled embodiments as in claims 61-63).

6. This application contains claims 26-35, 50, 61-63, 84, 86-93 and 95-97 drawn to a nonelected invention. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Drawings

7. The corrected or substitute drawings were received on 9/29/03. These drawings have been entered.

Outstanding Objection(s) and/or Rejection (s)

Claim Rejections - 35 USC § 103

8. Claims 46-49, 70-71, 73-83 and 85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yagi et al. US Pat. No. 5,061,691 (10/91) and Ekwuribe US Pat. No. 5,681,811 (10/97: filed 7/95 or earlier) and further in view of the specification (e.g. abstract; page 2 and Examples, especially on pages 44-48) as evidence of inherency.

Yagi et al. teach the induction of analgesia by opioids (e.g endorphins/enkephalins) and the making of analogs of the peptide opioids Met- and Leu-enkephalins in order to promote *in vivo* delivery by overcoming art-recognized administration obstacles (e.g. enzymatic degradation; ability to pass thru blood-brain barrier; administration in oral dosage form etc.). See abstract; col. 1; and patent claims.

The Yagi et al. reference teaching differs from the presently claimed invention which achieves analgesic therapy (e.g enteral/parenteral administration) of opioids (e.g. especially peptide opioids Met- and Leu-enkephalins) by conjugating the opioids (especially enkephalins) with a polymer which comprises lipophilic and hydrophilic moieties.

However, Ekwuribe teaches the stabilization of "therapeutic agents" (E.g. protease resistance and enhanced penetration) for in vivo administration (e.g. oral or parenteral) by conjugating with a polymer which comprises lipophilic and hydrophilic moieties. E.g. see abstract; col 1-4 (e.g. stabilization). Opioids, especially peptidic opioids such as endorphins and enkephalins are preferred "therapeutic agents". See Abstract; col. 8 (lines 40-50); patent claims (especially claims 37-44). Therapeutic administration includes administration to humans via enteral (e.g. oral), parenteral, as well as "other modes of physiological administration" (E.g. see col. 12, especially lines 5-10; col. 13, especially lines 45-55; col. 24-col. 24) including opthalmic, topical, bronchial, rectal, iv, subcutaneous, intrathecal etc (e.g. see col. 25-26). See also patent claims 35-44.

One of ordinary skill in the art would have been motivated to conjugate opioids (e.g. especially peptide opioids Met- and Leu-enkephalins and analogs thereof) as disclosed in Yagi et al. in the manner of Ekuwuribe to achieve an analgesic composition overcoming the *in vivo* obstacles recited in the Yagi reference.

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to achieve opioid (e.g. enkephalin) analgesic therapy by modifying the opioid with polymers comprising lipophilic and hydrophobic moieties as taught by Ekwuribe in order to obtain "stable therapeutic agents" for in vivo parenteral/enteral delivery.

To the extent the presently claimed invention (e.g. claims 48-49, 83, 85) selects PEG (as hydrophilic moiety; preferably PEG2) and C1-C26 (as lipophilic moiety) the same is rendered obvious by Ekwuribe.

Ekwuribe teaches the preferential selection of PEG (especially PEG2-4) as the hydrophilic moiety and alkyls (e.g. CH3 and CH2mCH3 m is 1-125) as the lipophilic moiety in which the "Drug is attached through a carbamate linkage adjacent to the PEG region of the polymer" with "the point of attachment of the carbamate bond between the polymers preferably is the amine function" . See col. 13-14, especially col. 13 (lines 5-20); col. 14 (conjugates 2 and 3); col 14 (lines 30-60); patent claims (especially claims 34 and conjugates 2 and 3 described therein and claims 35-42 drawn to therapeutic methods employing enkephalin conjugates). Ekuwuribe further teaches the ability to vary the position and number of hydrophilic/lipophilic moieties to achieve optimization. E.g. see col. 14, lines 50-60.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to utilize an oligomer (or polymer) comprising PEG (e.g. PEG2) as a hydrophilic moiety and a C1-26 alkyl in light of the Ekwuribe teaching of the preferred selection of PEG2-4 as a hydrophilic moiety and alkyls (e.g. m is 1-125 with methyl disclosed) with optimization of hydrophilic/lipophilic groups suggested by Ekwuribe in which such optimization is well within the skill of the art.

Additionally, the Yagi et al. reference differs (if at all) from the presently claimed invention (as amended) by failing to disclose or suggest that administration of an *amphiplic drug-oligomer conjugate* within the scope of the presently claimed invention which achieves "delivery (of the conjugate) across the blood brain barrier of the subject".

However, in this respect it is first noted that the Yagi et al. Reference teaches that the molecular structure of synthetic enkephalins are designed to yield enkephalins which cross the blood-brain barrier. Accordingly, conjugate modification utilizing the Ekwuribe method would engender a *reasonable expectation* of achieving a conjugated enkephalin possessing not only the benefits of conjugation taught by Ekwuribe but also retention of the ability of the unconjugated peptides to cross the blood brain barrier since Ekwuribe teaches that the biological activity of its conjugated therapeutic compounds is retained following conjugation.

Additionally, the presently claimed method rendered obvious by the above-recited references, must inherently produce the same *in vivo* effect (blood brain barrier delivery) because the same conjugate is applied (e.g. administered) in the same way in

the same amount to the same subject. *In re Best*, 195 USPQ 430,433 (CCPA 1977). The specification provides evidence that the amphiphilic oligomer conjugates rendered obvious by the above references, are capable of (e.g. see present specification on page 2 and abstract) and indeed do traverse the blood brain barrier upon administration to subjects in the manner taught by the prior art references. See ***Ex parte Novitski***, 26 USPQ2d 1389 (B.P.A.I, 1993) (applicant's own specification provides evidence of inherent effect produced upon drug administration); MPEP 2131.01(d) permits the citation of references or any other source of extrinsic evidence in order to show that a characteristic not disclosed in the reference is inherent.

9. Claims 46-49, 70-71, 73-83 , 85 and 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yagi et al. US Pat. No. 5,061,691 (10/91), Ekwuribe US Pat. No. 5,681,811 (10/97: filed 7/95 or earlier) and the specification as applied to claims 46-49, 70-71, 73-83 , 85 above, and further in view of Mensi-Fattohi et al. US Pat. No. 5,428, 128 (6/95).

The combined obviousness teaching of the Yagi and Ekwuribe patent references as discussed in the above rejection is hereby incorporated by reference in its entirety.

The combined teaching of Yagi and Ekwuribe further differ from the presently claimed (e.g. claim 94) which uses as therapeutic agent, Met-enkephalin modified by carboxyl addition of a lysine to effect Polyethylene glycol-alkyl attachment through a carbamate linkage via the epsilon aminolysine sidechain (e.g. Tyr-Gly-Gly-Phe-Met is Met-enkephalin) .

Initially, it is noted that Ekwuribe specifically suggests that the PEG of the oligomer be carbamate attached via an amino group to the polymer. E.e. see Ekwuribe at col. 14. In this regard, the Mensi-Fatthohi et al. reference teaches the carbamate attachment of PEG to opioid peptides thru a Lysine epsilon amino group in which the lysine is initially present or subsequently added to the opioid peptide. See Mensi-Fatthohi at col. 4 (lines 1-10; 20-40); examples, especially examples 9-10; and patent claims 1-29.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to further modify the enkephalin (e.g. Met-enkephalin) containing PEG-alkyl conjugates to attach (via a carbamate bond) by the use of an lysine epsilon amino group as taught by Mensi-Fatthohi in light of the Ekwuribe teaching of using amino groups for carbamate PEG attachment.

Discussion

Applicant's arguments directed to the above obviousness rejections were considered but deemed nonpersuasive for the following reasons. Initially, it is noted that the above rejections were modified in response to applicant's amendment.

Applicant argues that Ekwuribe '811 although teaching chemical drug modification to promote cell membrane penetration fails to teach/suggest such modification to promote blood brain drug delivery. Additionally, with respect to the Yagi reference applicant argues that its teaching of the beneficial (e.g. designed) ability of unconjugated enkephalin to cross the blood brain barrier does not provide motivation to conjugate enkephalin to promote blood-brain barrier crossing; but in fact teaches away

from the presently claimed invention. Theses arguments are not persuasive for several reasons.

In response to applicant's arguments against the Ekwuribe '811 and Yagi et al. references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

It is indeed noted that the Yagi et al. Reference teaches that the molecular structure of synthetic enkephalins are designed to yield enkephalins which cross the blood-brain barrier. Accordingly, conjugate modification utilizing the Ekwuribe method would engender a *reasonable expectation* of achieving a conjugated enkephalin possessing not only the benefits of conjugation taught by Ekwuribe but also retention of the ability of the unconjugated peptides to cross the blood brain barrier since Ekwuribe teaches that the biological activity of its conjugated therapeutic compounds is retained following conjugation. Additionally, with respect to obviousness, applicant is directed to the CAFC case of *In re Dillon*, 16 USPQ2d 1897 (CA FC 1990) which held that the motivation to combine references need not be the same as applicant's to render obvious the presently claimed invention. Accordingly, the motivation to conjugate the Yagi reference compounds for the benefits (exclusive of blood brain delivery) elucidated in the Ekwuribe reference is sufficient in itself to render the presently claimed invention obvious. Thus, the fact that applicant has recognized another advantage (blood brain delivery of conjugated peptide) which would flow naturally from following the

suggestion of the prior art (e.g. to conjugate) cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). The fact that the prior art already recognizes that unconjugated peptide beneficially achieves blood brain delivery upon administration is a teaching toward not away from the presently claimed invention; since this benefit would be reasonably expected to be retained as an added benefit upon conjugation in light of the Ekwuribe method's ability to retain therapeutic utility upon conjugation.

Applicant further argues (citing a reference) that the blood brain barrier acts to exclude (e.g. endothelial capillary cells etc.) certain molecules; and applicant additionally cites a statement of allowable subject matter recited by a patent examiner in the parent 09/134,803 application regarding the Ekwuribe '811 reference's lack of teaching its conjugates ability to traverse the blood brain barrier. This argument is not persuasive for several reasons.

Initially, it is noted that the cited article is NOT directed to opioids which possess the ability to cross the blood-brain barrier as taught by the Yagi reference.

Secondly, it is noted that the above prior art rejections, which include the Yagi reference teaching of the ability of unconjugated opioid to cross the blood-brain barrier was at issue, was not at issue in the parent application. Thirdly, the issue of the inherent ability of the present method to result in blood brain delivery of the conjugated opioid compound was similarly not at issue in the parent application..

As discussed in the modified rejections above, the Yagi et al. Reference teaches that the molecular structure of synthetic enkephalins are designed to yield enkephalins

which cross the blood-brain barrier. Accordingly, conjugate modification utilizing the Ekwuribe method would engender a *reasonable expectation* of achieving a conjugated enkephalin possessing not only the benefits of conjugation taught by Ekwuribe but also retention of the ability of the unconjugated peptides to cross the blood brain barrier since Ekwuribe teaches that the biological activity of its conjugated therapeutic compounds is retained following conjugation. Accordingly, the retained ability of the conjugated opioid compounds to traverse the blood-brain barries is hardly unexpected.

Further, the presently claimed method rendered obvious by the above-recited references, must inherently produce the same *in vivo* effect (blood brain barrier delivery) because the same conjugate is applied (e.g. administered) in the same way in the same amount to the same subject. *In re Best*, 195 USPQ 430,433 (CCPA 1977). The specification provides evidence that the amphiphilic oligomer conjugates rendered obvious by the above references, are capable of (e.g. see present specification on page 2 and abstract) and indeed do traverse the blood brain barrier upon administration to subjects in the manner taught by the prior art references. See ***Ex parte Novitski***, 26 USPQ2d 1389 (B.P.A.I, 1993) (applicant's own specification provides evidence of inherent effect produced upon drug administration); MPEP 2131.01(d) permits the citation of references or any other source of extrinsic evidence in order to show that a characteristic not disclosed in the reference is inherent.

Accordingly, the above obviousness rejections are hereby maintained.

Double Patenting

10. Claims 46-47, 70-71 and 73-82 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-60 of U.S. Patent No. 6,309,633 (10/01) in view of Yagi et al. US Pat. No. 5,061,691 (10/91) and further in view of the present specification (e.g. abstract; page 2 and Examples, especially on pages 44-48) as evidence of inherency.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent claims teaches conjugates and pharmaceutical compositions and the administration thereof which comprise a drug oligomer complex in which the oligomer comprises a hydrophilic portion (E.g. PEG) and a hydrophobic portion (e.g. alkyl chain) in which the claimed drug can be selected from a group of preferred drugs which include opioids (e.g. see claim 34 which includes dynorphins, endorphins and enkaphilins) the selection of which would have been obvious since these represent most preferred (e.g. claimed) drug embodiments. The analgesic therapeutic use of the patented therapeutic compositions would have been obvious to one of ordinary skill in the art at the time of applicant's invention upon *in vivo* delivery as taught by the Yagi et al. reference.

Additionally, the teaching of the '633 patent claims differ from the presently claimed invention (as amended) by failing to disclose or suggest that administration of an amphiplic drug-oligomer conjugate within the scope of the presently claimed

invention achieves "delivery (of the conjugate) across the blood brain barrier of the subject".

However, in this respect it is first noted that the Yagi et al. Reference (e.g. col. 1, particularly paragraph 4) teaches that the molecular structure of synthetic enkephalins are designed to yield enkephalins which cross the blood-brain barrier. Accordingly, conjugate modification utilizing the Ekwuribe method would engender a *reasonable expectation* of achieving a conjugated enkephalin possessing not only the benefits of conjugation taught by Ekwuribe but also retention of the ability of the unconjugated peptides to cross the blood brain barrier since Ekwuribe teaches that the biological activity of its conjugated therapeutic compounds is retained following conjugation.

Additionally, the presently claimed method rendered obvious by the above-recited patents and references, must inherently produce the same *in vivo* effect (blood brain barrier delivery) because the same conjugate is applied (e.g. administered) in the same way in the same amount to the same subject. *In re Best*, 195 USPQ 430,433 (CCPA 1977). The specification provides evidence that the amphiphilic oligomer conjugates rendered obvious by the above references, are capable of (e.g. see present specification on page 2 and abstract) and indeed do traverse the blood brain barrier upon administration to subjects in the manner taught by the prior art references. See ***Ex parte Novitski***, 26 USPQ2d 1389 (B.P.A.I, 1993) (applicant's own specification provides evidence of inherent effect produced upon drug administration); MPEP 2131.01(d) permits the citation of references or any other source of extrinsic evidence in order to show that a characteristic not disclosed in the reference is inherent.

11. Claims 46-49, 70-71, 73-83 , 85 and 94 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-60 of U.S. Patent No. 6,309,633 (10/01)and Yagi et al. US Pat. No. 5,061,691 (10/91). in view of Ekuwuribe US Pat. No. 5,681,811 alone and further in view of Mensi-Fattohi et al. US Pat. No. 5,428, 128 (6/95) and further in view of the present specification (e.g. abstract; page 2 and Examples, especially on pages 44-48) as evidence of inherency.

The combined '633 patent and Yagi patent obviousness teaching of the these reference recited above is hereby incorporated by reference in its entirety.

To the extent the presently claimed invention (e.g. claims 48-49, 83, 85) selects PEG (as hydrophilic moiety; preferably PEG2) and C1-C26 (as lipophilic moiety) the same is rendered obvious by Ekwuribe.

Ekwuribe teaches the preferential selection of PEG (especially PEG2-4) as the hydrophilic moiety and alkyls (e.g. CH3 and CH2mCH3 m is 1-125) as the lipophilic moiety in which the "Drug is attached through a carbamate linkage adjacent to the PEG region of the polymer" with "the point of attachment of the carbamate bond between the polymers preferably is the amine function" . See col. 13-14, especially col. 13 (lines 5-20); col. 14 (conjugates 2 and 3); col 14 (lines 30-60); patent claims (especially claims 34 and conjugates 2 and 3 described therein and claims 35-42 drawn to therapeutic methods employing enkephalin conjugates). Ekwuribe further teaches the ability to vary the position and number of hydrophilic/lipophilic moieties to achieve optimization. E.g. see col. 14, lines 50-60.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to utilize an oligomer (or polymer) comprising PEG (e.g. PEG2) as a hydrophilic moiety and a C1-26 alkyl in light of the Ekwuribe teaching of the preferred selection of PEG2-4 as a hydrophilic moiety and alkyls (e.g. m is 1-125 with methyl disclosed) with optimization of hydrophilic/lipophilic groups suggested by Ekwuribe in which such optimization is well within the skill of the art.

The combined teaching of patent '633, Yagi and Ekwuribe further differ from the presently claimed (e.g. claim 94) which uses as therapeutic agent, Met-enkephalin modified by carboxyl addition of a lysine to effect Polyethylene glycol-alkyl attachment through a carbamate linkage via the epsilon aminolysine sidechain (e.g. Tyr-Gly-Gly-Phe-Met is Met-enkephalin) .

Initially, it is noted that Ekwuribe specifically suggests that the PEG of the oligomer be carbamate attached via an amino group to the polymer. E.e. see Ekwuribe at col. 14. In this regard, the Mensi-Fatthohi et al. reference teaches the carbamate attachment of PEG to opioid peptides thru a Lysine epsilon amino group in which the lysine is initially present or subsequently added to the opioid peptide. See Mensi-Fatthohi at col. 4 (lines 1-10; 20-40); examples, especially examples 9-10; and patent claims 1-29.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to further modify the enkephalin (e.g. Met-enkephalin) containing PEG-alkyl conjugates to attach (via a carbamate bond) by the

use of an lysine epsilon amino group as taught by Mensi-Fatthohi in light of the Ekwuribe teaching of using amino groups for carbamate PEG attachment.

Additionally, the teaching of the '633 patent claims differ from the presently claimed invention (as amended) by failing to disclose or suggest that administration of an amphiplic drug-oligomer conjugate within the scope of the presently claimed invention achieves "delivery (of the conjugate) across the blood brain barrier of the subject".

However, in this respect it is first noted that the Yagi et al. Reference teaches (e.g. see col. 1, particularly paragraph 4) that the molecular structure of synthetic enkephalins are designed to yield enkephalins which cross the blood-brain barrier. Accordingly, conjugate modification utilizing the Ekwuribe method would engender a *reasonable expectation* of achieving a conjugated enkephalin possessing not only the benefits of conjugation taught by Ekwuribe but also retention of the ability of the unconjugated peptides to cross the blood brain barrier since Ekwuribe teaches that the biological activity of its conjugated therapeutic compounds is retained following conjugation.

Additionally, the presently claimed method rendered obvious by the above-recited patents and references, must inherently produce the same *in vivo* effect (blood brain barrier delivery) because the same conjugate is applied (e.g. administered) in the same way in the same amount to the same subject. *In re Best*, 195 USPQ 430,433 (CCPA 1977). The specification provides evidence that the amphiphilic oligomer conjugates rendered obvious by the above references, are capable of (e.g. see present

specification on page 2 and abstract) and indeed do traverse the blood brain barrier upon administration to subjects in the manner taught by the prior art references. See ***Ex parte Novitski***, 26 USPQ2d 1389 (B.P.A.I, 1993) (applicant's own specification provides evidence of inherent effect produced upon drug administration); MPEP 2131.01(d) permits the citation of references or any other source of extrinsic evidence in order to show that a characteristic not disclosed in the reference is inherent.

12. Claims 46-49, 70-71, 73-83 and 85 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-44 of Ekwuribe US Pat. No. 5,681,811 (10/97: filed 7/95 or earlier) and Yagi et al. US Pat. No. 5,061,691 (10/91); and further in view of the present specification (e.g. abstract; page 2 and Examples, especially on pages 44-48) as evidence of inherency.

The Ekwuribe '811 patent claims teach the stabilization of "therapeutic agents" (E.g. protease resistance and enhanced penetration) for in vivo administration (e.g. oral or parenteral) by conjugating with a polymer which comprises lipophilic and hydrophilic moieties; with opioids, especially peptidic opioids such as endorphins and enkephalins being preferred "therapeutic agents". See e.g. patent claims (especially claims 37-44). The Claimed therapeutic administration includes administration to humans via enteral (e.g. oral), parenteral, as well as "other modes of physiological administration" (E.g. see col. 12, especially lines 5-10; col. 13, especially lines 45-55; col. 24-col. 24) including ophthalmic, topical, bronchial, rectal, iv, subcutaneous, intrathecal etc (e.g. see col. 25-26). See also patent claims 35-44. The analgesic therapeutic use of the patented

therapeutic compositions would have been obvious to one of ordinary skill in the art at the time of applicant's invention upon *in vivo* delivery as taught by the Yagi et al. reference which teaches the induction of analgesia by opioids (e.g endorphins/enkephalins) and the making of analogs of the peptide opioids Met- and Leu-enkephalins in order to promote *in vivo* delivery by overcoming art-recognized administration obstacles (e.g. enzymatic degradation; ability to pass thru blood-brain barrier; administration in oral dosage form etc.). See abstract; col. 1; and patent claims.

To the extent the presently claimed invention (e.g. claims 48-49, 83, 85) selects PEG (as hydrophilic moiety; preferably PEG2) and C1-C26 (as lipophilic moiety) the same is rendered obvious by Ekwuribe.

Ekwuribe teaches the preferential selection of PEG (especially PEG2-4) as the hydrophilic moiety and alkyls (e.g. CH3 and CH2mCH3 m is 1-125) as the lipophilic moiety in which the "Drug is attached through a carbamate linkage adjacent to the PEG region of the polymer" with "the point of attachment of the carbamate bond between the polymers preferably is the amine function" . See col. 13-14, especially col. 13 (lines 5-20); col. 14 (conjugates 2 and 3); col 14 (lines 30-60); patent claims (especially claims 34 and conjugates 2 and 3 described therein and claims 35-42 drawn to therapeutic methods employing enkephalin conjugates). Ekwuribe further teaches the ability to vary the position and number of hydrophilic/lipophilic moieties to achieve optimization. E.g. see col. 14, lines 50-60.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to utilize an oligomer (or polymer) comprising

PEG (e.g. PEG2) as a hydrophilic moiety and a C1-26 alkyl in light of the Ekwuribe teaching of the preferred selection of PEG2-4 as a hydrophilic moiety and alkyls (e.g. m is 1-125 with methyl disclosed) with optimization of hydrophilic/lipophilic groups suggested by Ekwuribe in which such optimization is well within the skill of the art.

Additionally, the teaching of the '811 patent claims differ from the presently claimed invention (as amended) by failing to disclose or suggest that administration of an amphiplic drug-oligomer conjugate within the scope of the presently claimed invention achieves "delivery (of the conjugate) across the blood brain barrier of the subject".

However, in this respect it is first noted that the Yagi et al. Reference teaches (e.g. see col. 1, particularly paragraph 4) that the molecular structure of synthetic enkephalins are designed to yield enkephalins which cross the blood-brain barrier. Accordingly, conjugate modification utilizing the Ekwuribe method would engender a *reasonable expectation* of achieving a conjugated enkephalin possessing not only the benefits of conjugation taught by Ekwuribe but also retention of the ability of the unconjugated peptides to cross the blood brain barrier since Ekwuribe teaches that the biological activity of its conjugated therapeutic compounds is retained following conjugation.

Additionally, the presently claimed method rendered obvious by the above-recited patents and references, must inherently produce the same *in vivo* effect (blood brain barrier delivery) because the same conjugate is applied (e.g. administered) in the same way in the same amount to the same subject. *In re Best*, 195 USPQ 430,433

(CCPA 1977). The specification provides evidence that the amphiphilic oligomer conjugates rendered obvious by the above references, are capable of (e.g. see present specification on page 2 and abstract) and indeed do traverse the blood brain barrier upon administration to subjects in the manner taught by the prior art references. See ***Ex parte Novitski***, 26 USPQ2d 1389 (B.P.A.I, 1993) (applicant's own specification provides evidence of inherent effect produced upon drug administration); MPEP 2131.01(d) permits the citation of references or any other source of extrinsic evidence in order to show that a characteristic not disclosed in the reference is inherent.

13. Claims 46-49, 70-71, 73-83 , 85 and 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ekwuribe US Pat. No. 5,681,811 (10/97: filed 7/95 or earlier) and Yagi et al. US Pat. No. 5,061,691 (10/91) as applied to claims 46-49, 70-71, 73-83 , 85 above, and further in view of Mensi-Fattohi et al. US Pat. No. 5,428, 128 (6/95); and still further in view of the present specification (e.g. abstract; page 2 and Examples, especially on pages 44-48) as evidence of inherency.

The combined obviousness teaching of the Yagi and Ekwuribe patent claims as discussed in the above rejection is hereby incorporated by reference in its entirety.

The combined teaching of Yagi and Ekwuribe further differ from the presently claimed (e.g. claim 94) which uses as therapeutic agent, Met-enkephalin modified by carboxyl addition of a lysine to effect Polyethylene glycol-alkyl attachment through a carbamate linkage via the epsilon aminolysine sidechain (e.g. Tyr-Gly-Gly-Phe-Met is Met-enkephalin) .

Initially, it is noted that Ekwuribe specifically suggests that the PEG of the oligomer be carbamate attached via an amino group to the polymer. E.e. see Ekwuribe at col. 14. In this regard, the Mensi-Fatthohi et al. reference teaches the carbamate attachment of PEG to opioid peptides thru a Lysine epsilon amino group in which the lysine is initially present or subsequently added to the opioid peptide. See Mensi-Fatthohi at col. 4 (lines 1-10; 20-40); examples, especially examples 9-10; and patent claims 1-29.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to further modify the enkephalin (e.g. Met-enkephalin) containing PEG-alkyl conjugates to attach (via a carbamate bond) by the use of an lysine epsilon amino group as taught by Mensi-Fatthohi in light of the Ekwuribe teaching of using amino groups for carbamate PEG attachment.

Additionally, the teaching of the '811 patent claims differ from the presently claimed invention (as amended) by failing to disclose or suggest that administration of an amphiplic drug-oligomer conjugate within the scope of the presently claimed invention achieves "delivery (of the conjugate) across the blood brain barrier of the subject".

However, in this respect it is first noted that the Yagi et al. Reference teaches (e.g. see col. 1, particularly paragraph 4) that the molecular structure of synthetic enkephalins are designed to yield enkephalins which cross the blood-brain barrier. Accordingly, conjugate modification utilizing the Ekwuribe method would engender a *reasonable expectation* of achieving a conjugated enkephalin possessing not only the

benefits of conjugation taught by Ekwuribe but also retention of the ability of the unconjugated peptides to cross the blood brain barrier since Ekwuribe teaches that the biological activity of its conjugated therapeutic compounds is retained following conjugation.

Additionally, the presently claimed method rendered obvious by the above-recited patents and references, must inherently produce the same *in vivo* effect (blood brain barrier delivery) because the same conjugate is applied (e.g. administered) in the same way in the same amount to the same subject. *In re Best*, 195 USPQ 430,433 (CCPA 1977). The specification provides evidence that the amphiphilic oligomer conjugates rendered obvious by the above references, are capable of (e.g. see present specification on page 2 and abstract) and indeed do traverse the blood brain barrier upon administration to subjects in the manner taught by the prior art references. See ***Ex parte Novitski***, 26 USPQ2d 1389 (B.P.A.I, 1993) (applicant's own specification provides evidence of inherent effect produced upon drug administration); MPEP 2131.01(d) permits the citation of references or any other source of extrinsic evidence in order to show that a characteristic not disclosed in the reference is inherent.

14. Claims 46-49, 70-71, 73-83 and 85 are rejected under the judicially created doctrine of provisional obviousness-type double patenting as being unpatentable over the claims (e.g. claims 46-52) of Ekwuribe et al. 09/429,798; and still further in view of the present specification (e.g. abstract; page 2 and Examples, especially on pages 44-48) as evidence of inherency.

The Ekwuribe claims teach the analgesic administration of "therapeutic agents" (E.g. drug oligomer conjugates by conjugating with a polymer which comprises lipophilic and hydrophilic moieties; with opioids, especially peptidic opioids such as endorphins and enkephalins being preferred. See e.g. the claims (especially claims 46-52). The Claimed therapeutic administration includes administration to humans via enteral (e.g. oral), parenteral, as well as "other modes of physiological administration" (E.g. see specification).

To the extent the presently claimed invention (e.g. claims 48-49, 83, 85) selects PEG (as hydrophilic moiety; preferably PEG2) and C1-C26 (as lipophilic moiety) the same is rendered obvious by Ekwuribe. Ekwuribe teaches the preferential selection of PEG (especially PEG2-4) as the hydrophilic moiety and alkyls (e.g. CH3 and CH2mCH3 m is 1-125) as the lipophilic moiety in (e.g. the drug is attached through a carbamate linkage adjacent to the PEG region of the polymer with the point of attachment of the carbamate bond between the polymers preferably is the amine function)

Additionally, the teaching of the '798 application claims differ (if at all) from the presently claimed invention (as amended) by failing to disclose or suggest that administration of an amphiplic drug-oligomer conjugate within the scope of the presently claimed invention achieves "delivery (of the conjugate) across the blood brain barrier of the subject".

However, the presently claimed method rendered obvious by the above-recited application claims, must inherently produce the same *in vivo* effect (blood brain barrier delivery) because the same conjugate is applied (e.g. administered) in the same way in

the same amount to the same subject. *In re Best*, 195 USPQ 430,433 (CCPA 1977). The specification provides evidence that the amphiphilic oligomer conjugates rendered obvious by the above references, are capable of (e.g. see present specification on page 2 and abstract) and indeed do traverse the blood brain barrier upon administration to subjects in the manner taught by the prior art references. See ***Ex parte Novitski***, 26 USPQ2d 1389 (B.P.A.I, 1993) (applicant's own specification provides evidence of inherent effect produced upon drug administration); MPEP 2131.01(d) permits the citation of references or any other source of extrinsic evidence in order to show that a characteristic not disclosed in the reference is inherent.

15. Claims 46-49, 70-71, 73-83 , 85 and 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ekwuribe et al. 09/429,798. as applied to claims 46-49, 70-71, 73-83 , 85 above, and further in view of Ekwuribe US Pat. No. 5,681,811 (10/97: filed 7/95 or earlier) and Mensi-Fattohi et al. US Pat. No. 5,428, 128 (6/95); and still further in view of the present specification (e.g. abstract; page 2 and Examples, especially on pages 44-48) as evidence of inherency.

The provisional obviousness teaching of the Ekwuribe patent application claims as discussed in the above rejection is hereby incorporated by reference in its entirety.

The Ekwuribe claims differ from the presently claimed (e.g. claim 94) which uses as therapeutic agent, Met-enkephalin modified by carboxyl addition of a lysine to effect Polyethylene glycol-alkyl attachment through a carbamate linkage via the epsilon aminolysine sidechain (e.g. Tyr-Gly-Gly-Phe-Met is Met-enkephalin) .

The Ekwuribe patent '811 teaches the preferential selection of PEG (especially PEG2-4) as the hydrophilic moiety and alkyls (e.g. CH3 and CH2mCH3 m is 1-125) as the lipophilic moiety in which the "Drug is attached through a carbamate linkage adjacent to the PEG region of the polymer" with "the point of attachment of the carbamate bond between the polymers preferably is the amine function" . See col. 13-14, especially col. 13 (lines 5-20); col. 14 (conjugates 2 and 3); col 14 (lines 30-60); patent claims (especially claims 34 and conjugates 2 and 3 described therein and claims 35-42 drawn to therapeutic methods employing enkephalin conjugates). Ekuwuribe '811 further teaches the ability to vary the position and number of hydrophilic/lipophilic moieties to achieve optimization. E.g. see col. 14, lines 50-60. Additionally, the Ekwuribe '811 patent specifically suggests that the PEG of the oligomer be carbamate attached via an amino group to the polymer. E.e. see Ekwuribe at col. 14.

In this regard, the Mensi-Fatthohi et al. reference teaches the carbamate attachment of PEG to opioid peptides thru a Lysine epsilon amino group in which the lysine is initially present or subsequently added to the opioid peptide. See Mensi-Fatthohi at col. 4 (lines 1-10; 20-40); examples, especially examples 9-10; and patent claims 1-29.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to further modify the enkephalin (e.g. Met-enkephalin) to contain PEG-alkyl conjugates as disclosed in the pending claims of 09/429,798 to attach (via a carbamate bond) by use of an lysine epsilon amino group

as taught by Mensi-Fatthohi in light of the Ekwuribe application and patent teaching of using amino groups for carbamate PEG attachment.

Additionally, the teaching of the '798 application claims differ (if at all) from the presently claimed invention (as amended) by failing to disclose or suggest that administration of an amphiphilic drug-oligomer conjugate within the scope of the presently claimed invention achieves "delivery (of the conjugate) across the blood brain barrier of the subject".

However, the presently claimed method rendered obvious by the above-recited application claims, must inherently produce the same *in vivo* effect (blood brain barrier delivery) because the same conjugate is applied (e.g. administered) in the same way in the same amount to the same subject. *In re Best*, 195 USPQ 430,433 (CCPA 1977). The specification provides evidence that the amphiphilic oligomer conjugates rendered obvious by the above references, are capable of (e.g. see present specification on page 2 and abstract) and indeed do traverse the blood brain barrier upon administration to subjects in the manner taught by the prior art references. See ***Ex parte Novitski***, 26 USPQ2d 1389 (B.P.A.I, 1993) (applicant's own specification provides evidence of inherent effect produced upon drug administration); MPEP 2131.01(d) permits the citation of references or any other source of extrinsic evidence in order to show that a characteristic not disclosed in the reference is inherent.

Discussion

Applicant's arguments directed to the above double patenting rejections were considered but deemed nonpersuasive for the following reasons. Initially, it is noted that the above rejections were modified in response to applicant's amendment.

Applicant's reiterate the arguments presented above in support of the position that the claimed invention is not obvious in view of the references alone or in combination. The Examiner similarly reiterated the above-cited rebuttal to applicant's arguments.

Applicant also indicates that terminal disclaimer(s), if necessary, will be submitted to obviate double patenting rejection upon the indication of allowable subject matter. Applicant's position regarding terminal disclaimer submission is duly noted.

Accordingly, the above double patenting rejections are hereby maintained.

Conclusion

16. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 703-305-7556. The examiner can normally be reached on 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 703-306-3217. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Bennett Celsa
Primary Examiner
Art Unit 1639

BC